

Packard

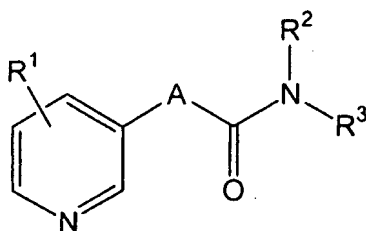
10/509,362

Attorney Docket 25846-0005

Amendments to the Claims:

1-14 Canceled.

15. (new) A method of inhibiting or reducing angiogenesis in a mammal comprising administering a compound of Formula I or a pharmaceutically acceptable salt thereof:



I

wherein:

A is selected from the group consisting of the group members C₁₋₁₀-alkylene, C₂₋₁₀-alkenylene, and C₂₋₁₀-alkynylene, which group members may be optionally substituted by one, two or three groups independently selected from C₁₋₃-alkyl, fluoro, chloro, and bromo;

R¹ is selected from hydrogen, C₁₋₆-alkyl, fluoro, chloro, bromo, and perfluoro-C₁₋₃-alkyl;

R² is selected from hydrogen, C₁₋₆-alkyl, and C₂₋₆-alkenyl; and

R³ is selected from the group consisting of the group members C₁₋₆-alkyl, (C₅₋₈-cycloalkyl)-C₁₋₆-alkyl, (C₅₋₈-heterocyclyl)-C₁₋₆-alkyl, C₁₋₆-alkyl (C₅₋₈-heterocyclyl)-C₁₋₆-alkyl, and C₁₋₅-alkylcarbonyl (C₅₋₈-heterocyclyl)-C₁₋₆-alkyl, which group members may be optionally substituted by one, two or three groups independently selected from C₁₋₆-alkyl, fluoro, chloro, bromo, oxo, perfluoro-C₁₋₃-alkyl, aryl, arylcarbonyl, heteroaryl, heteroarylcarbonyl, C₅₋₈-cycloalkyl and C₅₋₈-heterocyclyl.

16. (new) The method of claim 15, wherein A is selected from ethylene, n-propylene, i-propylene, n-butylene, ethenylene, 1-propenylene, 1-butenylene, 2-butenylene, and ethynylene.

17. (new) The method of claim 15, wherein R¹ is selected from hydrogen, methyl, ethyl, n-propyl, fluoro, and trifluoromethyl.

18. (new) The method of claim 15, wherein R² is selected from hydrogen, methyl, ethyl, n-propyl, and ethenyl.

19. (new) The method of claim 15, wherein R³ is selected from the group consisting of cyclopentyl-C₁₋₆-alkyl, cyclohexyl-C₁₋₆-alkyl, pyrrolidinyl-C₁₋₆-alkyl, piperidinyl-C₁₋₆-alkyl, C₁₋₆-alkyl-piperidinyl-C₁₋₆-alkyl, C₁₋₅-alkylcarbonyl piperidinyl-C₁₋₆-alkyl, piperazinyl-C₁₋₆-alkyl, C₁₋₆-alkyl-piperazinyl-C₁₋₆-alkyl, C₁₋₅-alkylcarbonyl-piperazinyl-C₁₋₆-alkyl, and morpholinyl-C₁₋₆-alkyl, which members may be optionally substituted by one, two or three groups independently selected from C₁₋₆-alkyl, fluoro, chloro, bromo, oxo, perfluoro-C₁₋₃-alkyl, aryl, arylcarbonyl, heteroaryl, C₅₋₈-cycloalkyl, and C₅₋₈-heterocyclyl.

20. (new) The method of claim 15, wherein R³ is selected from the group consisting of:

cyclohexyl-C₁₋₆-alkyl, piperidinyl-C₁₋₆-alkyl, C₁₋₆-alkyl piperidinyl-C₁₋₆-alkyl, C₁₋₅-alkylcarbonyl-piperidinyl-C₁₋₆-alkyl, piperazinyl-C₁₋₆-alkyl, C₁₋₆-alkyl-piperazinyl-C₁₋₆-alkyl, C₁₋₅-alkylcarbonyl-piperazinyl-C₁₋₆-alkyl, which members may be optionally substituted by one, two or three groups independently selected from butyl, pentyl, hexyl, fluoro, oxo, phenyl, biphenyl, benzyl, pyridyl, pyrrolyl, benzoyl, thiophenyl, furyl, cyclopentyl, cyclohexyl, and piperidinyl.

21. (new) The method of claim 15, wherein R³ is selected from the group consisting of

(1-acetyl-piperidin-4-yl)-butyl,

(1-diphenylacetyl-piperidin-4-yl)-butyl,
[1-(3,3-diphenylpropionyl)-piperidin-4-yl]butyl,
(1-benzoyl-piperidin-4-yl)-ethyl,
(1-benzoyl-piperidin-4-yl)-propyl,
(1-benzoyl-piperidin-4-yl)-butyl,
(1-benzoyl-piperidin-4-yl)-pentyl,
(1-benzoyl-piperidin-4-yl)-hexyl,
(1-benzylpiperidin-4-yl)-butyl,
(1-diphenylmethyl-piperidin-4-yl)-methyl,
(1-diphenylmethyl-piperidin-4-yl)-ethyl,
(1-diphenylmethyl-piperidin-4-yl)-propyl,
(1-diphenylmethyl-piperidin-4-yl)-butyl,
(1-diphenylmethyl-piperidin-4-yl)-pentyl,
(1-diphenylmethyl-piperidin-4-yl)-hexyl,
(4-phenyl-piperidin-1-yl)-butyl,
(4, 4-diphenyl-piperidin-1-yl)-butyl,
(1-benzoyl-2,6-dioxo-piperidin-4-yl)-butyl,
(2, 6-dioxo-3-phenyl-piperidin-1-yl)-butyl,
(2, 6-dioxo-4-phenyl-piperidin-1-yl)-butyl,
(4-phenyl-piperazin-1-yl)-butyl,
(4-phenyl-piperazin-1-yl)-pentyl,
(4-phenyl-piperazin-1-yl)-hexyl,
(4-diphenylacetyl-piperazin-1-yl)-butyl,
(4-benzoylpiperazin-1-yl)-butyl, and
(4-benzyl-2,6-dioxo-piperazin-1-yl)-butyl.

22. The method of claim 15, wherein the compound of Formula I is selected from the group consisting of:

N-[4-(1-acetyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-propionamide,

N-[4-(1-acetyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,
 N-[4-(1-diphenylacetyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,
 N-[4-(1-diphenylacetyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-propionamide,
 N-[4-(1-(3,3-diphenylpropionyl)-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,
 N-[3-(1-benzoyl-piperidin-4-yl)-propyl]-3-(pyridin-3-yl)-propionamide,
 N-[4-(1-benzoyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-propionamide,
 N-[6-(1-benzoyl-piperidin-4-yl)-hexyl]-3-(pyridin-3-yl)-propionamide,
 N-[2-(1-benzoyl-piperidin-4-yl)-ethyl]-3-(pyridin-3-yl)-acrylamide,
 N-[4-(1-benzoyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,
 N-[6-(1-benzoyl-piperidin-4-yl)-hexyl]-3-(pyridin-3-yl)-acrylamide,
 N-[4-(1-benzoyl-piperidin-4-yl)-butyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid amide,
 N-[4-(4-benzoyl-piperidin-1-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,
 N-[4-(4-benzoyl-piperidin-1-yl)-butyl]-3-(pyridin-3-yl)-propionamide,
 N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-propionamide,
 N-[4-(1-diphenylmethyl-piperidin-4-yl)-butyl]-3-(2-fluoropyridin-3-yl)-propionamide,
 N-[4-(1-diphenylmethyl-piperidin-4-yl)-butyl]-3-(5-fluoropyridin-3-yl)-propionamide,
 N-[4-(1-diphenylmethyl-piperidin-4-yl)-butyl]-2-fluoro-3-(pyridin-3-yl)-propionamide,
 N-[4-(1-diphenylmethyl-piperidin-4-yl)-butyl]-2,2-difluoro-3-(pyridin-3-yl)-
 propionamide,
 N-[5-(1-diphenylmethyl-piperidin-4-yl)-pentyl]-3-(pyridin-3-yl)-propionamide,
 N-[6-(1-diphenylmethyl-piperidin-4-yl)-hexyl]-3-(pyridin-3-yl)-propionamide,
 N-[2-(1-diphenylmethyl-piperidin-4-yl)-ethyl]-5-(pyridin-3-yl)-pentanoic acid amide,
 N-[4-(1-diphenylmethyl-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-propionamide,
 N-[4-(1-diphenylmethyl-piperidin-4-yl)-butyl]-5-(pyridin-3-yl)-pentanoic acid amide,
 N-[2-(1-diphenylmethylpiperidin-4-yl)-ethyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid
 amide,
 N-[4-(1-diphenylmethylpiperidin-4-yl)-butyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid
 amide,

N-[5-(1-diphenylmethylpiperidin-4-yl)-pentyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid
amide,

N-[6-(1-diphenylmethylpiperidin-4-yl)-hexyl]-5-(pyridin-3-yl)-2,4-pentadienoic acid
amide,

N-[4-(4-phenyl-piperidin-1-yl)-butyl]-3-pyridin-3-yl-acrylamide,

N-[4-(4,4-diphenyl-piperidin-1-yl)-butyl]-3-pyridin-3-yl-acrylamide,

N-[4-(1-benzoyl-2,6-dioxo-piperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,

N-[4-(2,6-dioxo-3-phenyl-piperidin-1-yl)-butyl]-3-pyridin-3-yl-acrylamide,

N-[4-(2,6-dioxo-4-phenyl-piperidin-1-yl)-butyl]-3-pyridin-3-yl-acrylamide,

N-[4-(4-benzoyl-piperazin-1-yl)-butyl]-3-(pyridin-3-yl)-acrylamide,

N-[4-(4-benzoyl-piperazin-1-yl)-butyl]-3-(pyridin-3-yl)-propionamide,

N-[4-(4-diphenylacetyl-piperazin-1-yl)-butyl]-3-pyridin-3-yl-acrylamide,

N-[4-(4-diphenylmethyl-piperazin-1-yl)-butyl]-3-pyridin-3-yl-propionamide,

N-[5-(4-diphenylmethyl-piperazin-1-yl)-pentyl]-3-pyridin-3-yl-acrylamide,

N-[6-(4-diphenylmethyl-piperazin-1-yl)-hexyl]-3-pyridin-3-yl-acrylamide,

N-[4-(4-diphenylmethyl-piperazin-1-yl)-butyl]-2-(pyridin-3-yl)-propionamide,

N-[4-(4-diphenylmethyl-piperazin-1-yl)-butyl]-5-(pyridin-3-yl)-penta-2,4-dienoic acid
amide, and

N-[4-(4-benzyl-2,6-dioxo-piperazin-1-yl)-butyl]-3-pyridin-3-yl-acrylamide.

23. (new) A method of treating a disease or medical condition in a mammal which
disease or medical condition responds to inhibition or reduction of angiogenesis,
comprising administering a compound of claim 15 or a pharmaceutically acceptable salt
thereof.

24. (new) The method of claim 23, wherein the disease or medical condition is
selected from rheumatoid arthritis, inflammatory disorder, macular degeneration,
psoriasis, retinopathy, preneoplastic lesions, and hyperplasia.

25. (new) The method of claim 24, wherein the disease or medical condition is selected from age-related macular degeneration, proliferative retinopathy, diabetic retinopathy, benign prostatic hyperplasia and venous neointimal hyperplasia.
26. (new) A method of treating a disease or medical condition in a mammal which disease or medical condition responds to inhibition or reduction of VEGF production, comprising administering a compound of claim 15 or a pharmaceutically acceptable salt thereof.
27. (new) A method of in vitro diagnosis of a disease or medical condition, which is selected from rheumatoid arthritis, inflammatory disorder, psoriasis, retinopathy, preneoplastic lesions, and hyperplasia, the method comprising obtaining a tumor from a warm blooded animal host, and implanting the tumor into mice to determine the decrease in growth after treatment with the compound of claim 15.
28. (new) The method of claim 27, wherein the disease or medical condition is selected from proliferative retinopathy, diabetic retinopathy, benign prostatic hyperplasia, and venous neointimal hyperplasia.
29. (new) A method of treating or preventing a disease or medical condition which disease or medical condition is selected from rheumatoid arthritis, inflammatory disorder; macular degeneration, psoriasis, retinopathy, preneoplastic lesions, and hyperplasia, the method comprising administering a pharmaceutical composition to a human or animal in need thereof, wherein the pharmaceutical composition comprises one or more of the compounds of Formula I or a pharmaceutically acceptable salt thereof, as defined according to claim 15, optionally together with (a) pharmaceutically acceptable carrier(s), (a) toxicologically safe adjuvant(s), and/or in combination with other active ingredients.
30. (new) The method of claim 29, wherein the disease or medical condition is selected from age-related macular degeneration, proliferative retinopathy, diabetic retinopathy, benign prostatic hyperplasia and venous neointimal hyperplasia.